# Significant Efficacy and Long-term Safety Difference With TAF-Based STR in Naïve Adults

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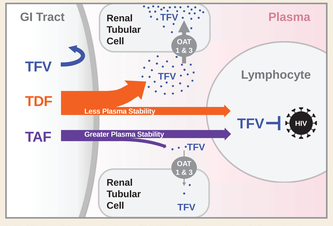
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## Introduction

- Two randomized, controlled, double-blinded, multinational Phase 3 trials (Studies 104 [NCT01780506] and 111 [NCT01797445]) compared the NRTIs tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF), each in single-tablet regimens coformulated with elvitegravir (E)/cobicistat (C)/emtricitabine (F)
- At Weeks 48 (primary endpoint) and 96, E/C/F/TAF had noninferior efficacy (HIV-1 RNA <50 copies/mL) to E/C/F/TDF, and less impact on bone and renal safety[1,2]
- We now present long-term (144-wk) efficacy, safety, and tolerability of treatment with E/C/F/TAF vs E/C/F/TDF in treatment-naive participants with HIV-1 from these trials

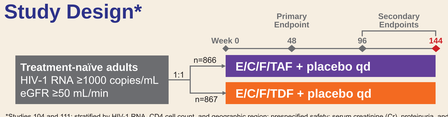
### Prodrug Pharmacology: TAF vs TDF*[1,3]




*TAF 25 mg results in 80–90% lower TFV plasma levels than TDF 300 mg. GI, gastrointestinal; OAT, organic anion transporter; TFV, tenofovir.

## Methods

### Study Design*




*Studies 104 and 111; stratified by HIV-1 RNA, CD4 cell count, and geographic region; prespecified safety: serum creatinine (Cr), proteinuria, and hip and spine bone mineral density (BMD). eGFR, estimated glomerular filtration rate.

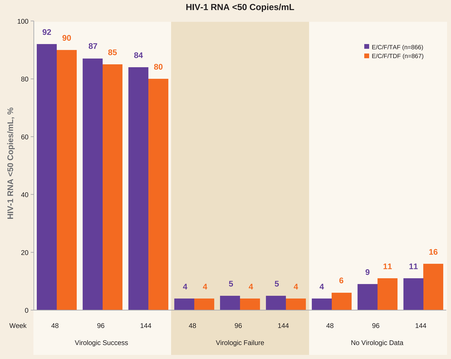
## Results

### Baseline Characteristics and Past Medical History

| | | E/C/F/TAF n=866 | E/C/F/TDF n=867 |
|---|---|---|---|
| Median age, yrs (range) | | 33 (18–74) | 35 (18–76) |
| Female, % | | 15 | 15 |
| Race and ethnicity, % | Black or African heritage | 26 | 25 |
| | Asian | 11 | 10 |
| | Hispanic or Latino | 19 | 19 |
| Median CD4 count, cells/μL | | 404 | 406 |
| CD4 <50 cells/μL, % | | 3 | 3 |
| HIV-1 RNA >100,000 copies/mL, % | | 23 | 22 |
| Median eGFR$_{CG}$, mL/min | | 117 | 114 |
| Medical history, % | Diabetes mellitus | 3 | 5 |
| | Hypertension | 14 | 17 |
| | Cardiovascular disease | 1 | 3 |
| | Hyperlipidemia | 11 | 12 |

CG, Cockcroft-Gault.

### Virologic Outcome at Weeks 48, 96, and 144*[1,2]



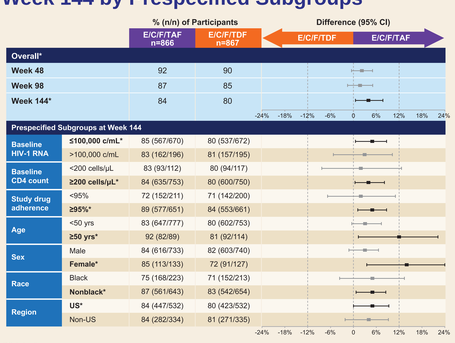

*By FDA snapshot analysis (12% noninferiority margin of TAF to TDF).

- At Week 144, E/C/F/TAF was superior to E/C/F/TDF in efficacy difference at both <50 copies/mL (4.2% [95% CI 0.6%, 7.8%; p=0.02]) and <20 copies/mL (5.4% [95% CI 1.5%, 9.2%; p=0.01])

### Resistance

- By 144 wk, virologic failure with resistance occurred in 24 participants: 12 (1.4%) on TAF vs 12 (1.4%) on TDF
- Genotypic resistance data: NRTI and EVG resistance (n=8) and NRTI resistance only (n=4) in the TAF group; NRTI and EVG resistance (n=7), NRTI resistance only (n=4), and EVG resistance only (n=1) in the TDF group

### Treatment Difference in Virologic Outcome at Week 144 by Prespecified Subgroups




*Statistically superior. c, copies.

### Renal Adverse Events Leading to Discontinuation

| Renal AE D/C, n* | E/C/F/TAF n=866 | E/C/F/TDF n=867 | p-Value† |
|---|---|---|---|
| Total | 0 | 12 | <0.001 |
| Proximal renal tubulopathy‡ | 0 | 4 | |
| Increased Cr/decreased eGFR | 0 | 3 | |
| Renal failure | 0 | 2 | |
| Nephropathy | 0 | 1 | |
| Proteinuria | 0 | 1 | |
| Bladder spasm | 0 | 1 | |

*Adverse events (AEs) coded as renal and urinary disorders (MedDRA 19.0); †Calculated using Fisher's exact test; ‡Renal tubular disorder, Fanconi syndrome/glycosuria.

- 0 case of proximal renal tubulopathy in E/C/F/TAF arm vs 4 in E/C/F/TDF arm
  - 2 additional cases in E/C/F/TDF arm since Week 96

### Week 144 Safety Summary*

| | Participants, n (%) | | E/C/F/TAF n=866 | E/C/F/TDF n=867 | p-Value† |
|---|---|---|---|---|---|
| Safety Summary | Any AE | | 817 (94.3) | 833 (96.1) | — |
| | Grade 3 or 4 AE | | 140 (16.2) | 137 (15.8) | — |
| | Serious AE | | 121 (14.0) | 124 (14.3) | — |
| | Death | | 4 (0.5)‡ | 5 (0.6)‡ | — |
| | AE-related D/C | Week 48 | 8 (0.9) | 13 (1.5) | 0.38 |
| | | Week 96 | 10 (1.2) | 20 (2.3) | 0.10 |
| | | Week 144 | 11 (1.3) | 29 (3.3) | 0.01 |
| AEs in ≥10% of Participants | Diarrhea | | 203 (23.4) | 212 (24.5) | — |
| | Upper respiratory tract infection | | 176 (20.3) | 170 (19.6) | — |
| | Headache | | 166 (19.2) | 135 (15.6) | — |
| | Nausea | | 150 (17.3) | 167 (19.3) | — |
| | Nasopharyngitis | | 125 (14.4) | 123 (14.2) | — |
| | Cough | | 117 (13.5) | 102 (11.8) | — |
| | Fatigue | | 101 (11.7) | 97 (11.2) | — |
| | Arthralgia | | 104 (12.0) | 82 (9.5) | — |
| | Back pain | | 104 (12.0) | 104 (12.0) | — |
| | Insomnia | | 94 (10.9) | 68 (7.8) | — |
| | Syphilis | | 86 (9.9) | 97 (11.2) | — |
| | Osteopenia | | 69 (8.0) | 87 (10.0) | — |

*Safety analysis set included all participants who received ≥1 dose; †Calculated using Fisher's exact test to compare treatment groups; ‡Stroke (n=2), alcohol intoxication (n=1), suicide (n=1); §Alcohol and drug intoxication (n=1), myocardial infarction (n=2), cardiac arrest (n=1), unknown (n=1). D/C, discontinuation.

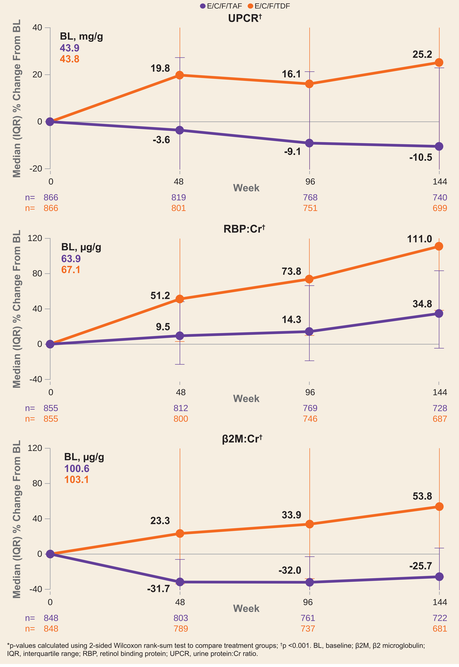
- AEs leading to D/C in the E/C/F/TAF group primarily happened early, whereas in the E/C/F/TDF group, AEs leading to D/C continued to accumulate, with a significant difference in total number of AEs at Week 144
- Most AEs occurred within first 4 wk of treatment initiation

### Week 144 Grade 3 or 4 Laboratory Abnormalities

| Participants, n (%) | E/C/F/TAF n=862* | E/C/F/TDF n=865* |
|---|---|---|
| Any Grade 3 or 4 lab abnormalities† | 284 (32.9) | 266 (30.7) |
| Creatine kinase elevation | 99 (11.5) | 87 (10.1) |
| LDL elevation (fasting) | 92/839 (11.0) | 40/834 (4.8) |
| Lipase‡ | 6/127 (5.0) | 13/154 (8.0) |
| Hypercholesterolemia (fasting) | 34/839 (4.7) | 23/835 (2.8) |
| AST | 29 (3.4) | 32 (4.0) |
| Amylase | 22 (2.6) | 43 (5.0) |
| Hematuria (quantitative) | 25 (2.9) | 26 (3.0) |
| Neutropenia | 16 (1.9) | 26 (3.0) |

*Denominator for percentage is number of participants in safety analysis set with ≥1 postbaseline lab value (for each test); †Occurring in ≥3% of participants in either group; ‡Lipase test was only performed for participants with serum amylase >1.5x upper limit of normal. AST, aspartate aminotransferase; LDL, low-density lipoprotein.

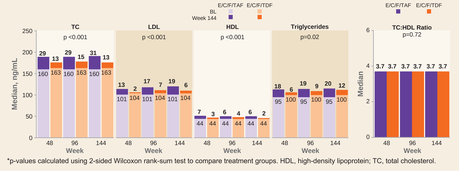
### Renal Parameters Through Week 144*




*p-values calculated using 2-sided Wilcoxon rank-sum test to compare treatment groups; †p <0.001. BL, baseline; β2M, β2 microglobulin; IQR, interquartile range; RBP, retinol binding protein; UPCR, urine protein:Cr ratio.

- At Week 144, median change from baseline in eGFR$_{CG}$ was significantly lower with E/C/F/TAF vs E/C/F/TDF (1.6 vs 7.7 mL/min; p<0.001)

### Fasting Lipids Through Week 144*




*p-values calculated using 2-sided Wilcoxon rank-sum test to compare treatment groups. HDL, high-density lipoprotein; TC, total cholesterol.

- Participants on E/C/F/TAF had greater increases in TC, LDL, and HDL than those on E/C/F/TDF, with no difference in rate of initiation of lipid-modifying agents (E/C/F/TAF: 5.5% [n=48]; E/C/F/TDF: 5.8% [n=50])

### Change in Spine and Hip BMD Through Week 144*




*p-values calculated using analysis of variance model including treatment as a fixed effect.

- Through Week 144, significantly greater losses in spine and hip BMD in TDF group
- No D/C due to bone AEs in TAF arm vs 6 in TDF arm

## Conclusions

- At Week 144, E/C/F/TAF was superior to E/C/F/TDF in virologic efficacy
  - HIV RNA <50 copies/mL: 84% vs 80%
  - HIV RNA <20 copies/mL: 81% vs 76%
- Emergence of resistance was rare
- E/C/F/TAF had significantly less impact than E/C/F/TDF on renal biomarkers
  - 0 vs 12 renal AEs; 0 vs 4 cases of proximal tubulopathy
- E/C/F/TAF had significantly less impact than E/C/F/TDF on BMD
  - 0 vs 6 D/C for bone loss
- These longer-term data support the use of E/C/F/TAF as a safe, well-tolerated, and durable regimen for initial and ongoing HIV-1 treatment

**References**

**1.** Sax P, et al. Lancet 2015;385:2606–15; **2.** Wohl D et al. J Acquir Immune Defic Syndr 2016;72:58–64; **3.** Sax P, et al. J Acquir Immune Defic Syndr 2014;67:52–8.

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